REMARKS/ARGUMENTS

Claims 1-2 and 9-17 are pending in the present case with the entry of this Amendment. Claim 1 has been amended and new claims 9-17 have been entered to better claim the subject matter which Applicants regard as the invention. Support is found throughout the Specification, particularly from page 7, line 10 to page 15, line 3, in the results shown in Figs. 1-4, Tables 1-4, and the Examples. Claims 3-8 have been canceled without prejudice. No new matter has been added with the present Amendment.

The as-filed Specification contains the updated priority information under the heading of "CROSS-REFERENCE TO RELATED APPLICATIONS" on the first page under the title. The date of publication for reference #13 (Mattson M.P.) is December 15, 1994.

Claim Rejections:

Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling. Without acquiescing to this rejection, claim 1 has been amended, claims 3-8 canceled without prejudice, and new claims 9-17 have been entered. Applicants respectfully traverse this rejection and provide the following comments.

The present invention is a method for identifying a compound as antioxidant by employing homozygous transgenic mice in which the genes encoding manganese superoxide dismutase (MnSOD) have been inactivated. The method involves administering a test compound to homozygous transgenic mice, MnSOD(-/-), and comparing the lifespan of such mice with that of the mice not treated with the compound. If the mice treated with a given compound have a longer lifespan than that of the untreated mice, the compound is then identified as antioxidant. The invention can also be practiced in conjunction with a known antioxidant. For example, a compound is

administered to the homozygous mice in combination with an antioxidant which is known to cross (or not cross) the blood brain barrier. In these instances, a compound is identified as antioxidant if the lifespan of the mice which were treated with the compound and the known antioxidant survived longer than the control mice which have been treated with only the known antioxidant. These methods are designed not only to identify compounds as having antioxidant activities but also to provide information about the compound identified regarding permeability of the blood brain barrier. The identification of such compounds offers a means of a selective treatment (CNS vs. non-CNS) of a variety of conditions, as illustrated in the Specification (see page 3, lines 4-17). The invention herein is based on the actual experimental results disclosed in the Specification, i.e., the inventors herein discovered that when the homozygous transgenic mice, SodCJE(-/-), were treated with two known antioxidants, MnTBAP and Euk-8, they survived significantly longer compared to those not treated with these compounds. Thus, the Specification as-filed provides sufficient description of the invention as claimed in such a way that a person of ordinary skill in the art can make and use the invention. In view of the amendments made herein, withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

The Office Action states:

> On page 16 the mice are reported to survive up to about 18 days and exhibit neuron degeneration without such treatment. This is in conflict with the data presented in Table 4 on page 30 which indicates the mice live about 7 days without treatment.

The present invention is based on the experimental results observed in the homozygous transgenic mice, SodCJE(-/-), in which the gene encoding Manganese Superoxide Dismutase (MnSOD) has been inactivated. As described on page 6, line 5 in the Specification, Li *et al.* reported that these mice die at about 10 days of age with

the range between 3 and 13 days of age (*See* page 7, line 1). Table 4 shows that the mean lifespan of the untreated mice is about 7 days in the experiments carried out by the inventors. Lebovitz *et al.* (1996) *Proc. Natl. Acad. Sci.* USA 93:9782-9787 (of record herein) reported another line of transgenic mice homozygous for the same enzyme, MnSOD, which survived up to about 18 days. Regardless of the reasons for the slight difference in the survival time between the two groups of homozygous transgenic mice, it is clear that the homozygous transgenic mice for MnSOD have a short lifespan. The invention claimed herein utilizes this short lifespan to identify a compound having antioxidant activity.

The Office Action asserts:

> In any case, it would appear to be essential to the invention to administer a free radical scavenger compound to the mice prior to the claimed screening (emphasis added).

The invention can be practiced with or without administering a free radical scavenger prior to the claimed method. Claims 1-2 and 9 define such methods. The methods defined by these claims would identify a compound that has antioxidant activity. The invention can also be practiced by coadministration of a test compound and a known antioxidant as defined in claims 10-17. The methods of claims 10-17 would identify compounds that have antioxidant activities but with different properties with respect to their effects on the central nervous system. The compounds identified by the methods of claims 10-13 are likely those that cross the blood brain barrier whereas the compounds identified by the methods of claims 14-17 are likely those that do not cross the blood brain barrier. Therefore, the invention serves as a means of identifying a variety of antioxidant compounds for different applications.

The Office Action further states that "it would appear following Li, mice would not live long enough to perform the presently claimed invention". It is not clear what the basis of this statement is. Both Li *et al.* and the present application show that the homozygous mice have the lifespan of about 10 days ranging approximately from the age 3 to 13 days. The examples (3 and 4) illustrated in the Specification used animals at about 3 days of age. The examples provided herein using the known antioxidants clearly indicate that the invention can be practiced using the mice described by Li *et al.*

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Li *et al.* Applicants respectfully traverse the rejection for the following reasons.

The Office Action alleges that Li *et al.* teaches mutant mice which produce inactive MnSOD and that this animal model is useful for studies on oxygen radical induced tissue injury. The Examiner acknowledges that the claims differ from Li in that they are directed to testing unknown compounds whereas Li teaches studying tissue injury with known compounds.

Applicants do not dispute that Li teaches the mutant mice, SodCJE(-/-), and that these mice can be a useful animal model for certain cases. However, there is nothing in Li *et al.* that suggests the use of these animals for testing unknown compounds to identify them as antioxidants. Li *et al.* merely provides a general statement concerning the potential utility of these animals. It is evident that these mice will be useful for studies on oxygen radical induced tissue injury. These mice lack MnSOD, a free radical scavenging enzyme. Accordingly, these mice are expected to exhibit oxygen radical induced tissue injury.

With the entry of this Amendment, the claims specifically define methods to identify a compound as antioxidant if the compound causes the homozygous mice survive longer than the untreated homozygous mice. This phenotype, i.e., longer

lifespan, could not have been known to or predicted by those skilled in the art unless the actual experimentation was carried out by employing the known antioxidants in these animals, as described in the present application. The inventors herein are the first to demonstrate this. Without this knowledge, a person of ordinary skill in the art would not have been able to make and use the invention.

Applicants do not agree with the following allegation made in the Office Action:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to test unknown compounds because Li teaches the transgenic mouse can be used for studying antioxidants in general and to study the antioxidants instead of their effects is an obvious variant.

Li *et al.* does not mention or suggest any antioxidants. Li *et al.* merely describes the homozygous mice and various characteristic phenotypes thereof. Nothing in Li *et al.* teaches or suggests any means to make these mice to live longer.

The Office Action states:

> It is the examiner's position that Li teaches homozygous mice are useful for the presently claimed invention, "Our animal model will be useful for studies on mitochondrial defect-related cardiomyopathy, oxygen radical induced tissue injury, cytokinin-mediated cellular responses and cellular differentiation."

Applicants emphasize that the claims as amended with the entry of the present Amendment define the methods of identifying a compound as having antioxidant activity

based on its effect on the lifespan of the homozygous mice for MnSOD. There is nothing in the above-quoted passage that suggests the invention.

In view of the amendments and the foregoing remarks, the invention as claimed is not *prima facie* obvious over Li *et al.* Withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

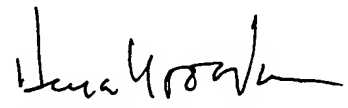
Conclusion:

Based on the foregoing amendments and arguments, this case is deemed to be in condition for allowance and passage to issuance is respectfully requested.

If there are further issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time and the required fees. If the amount submitted is incorrect, however, please refund or charge any fees necessary to Deposit Account No. 07-1969.

Respectfully submitted,



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